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10/517,453	12/09/2004	Ogari Pacheco	4705-0106PUS1	5587

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EXAMINER	
HUANG, GIGI GEORGIANA	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/517,453	PACHECO ET AL.	
	Examiner	Art Unit	
	GIGI HUANG	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,27,30,32-35 and 37-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27,30,32-35 and 37-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Status of Application

1. The response filed June 3, 2008 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claims 26-27, 30, 32-35 have been amended.

   b. Claim 1-2, 6, 8, 15-17, 19, 21-25, 28-29, 31, and 36 have been cancelled.

   c. Claims 37-45 have been added.

2. Claims 26-27, 30, 32-35, 37-45 are pending in the case.

3. Claims 26-27, 30, 32-35, 37-45 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 26-27, 30, 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of making a ritonavir composition wherein the amounts for the components used during the process of making are recited in percent weights with no context as to what it is a percent of. Additionally, Applicant states that the supports for the percent weights are from the original claims and the areas of the specification wherein the weight percents are to the final composition. However, there is no specific endpoint or final weight in the claims. Also, the *future percentages* cannot be utilize to estimate the amount of material such as ritonavir to be used *during* the method of making as it does not address how much ritonavir (e.g. milligrams) is used during the method. Specifically, ritonavir is placed with an alcoholic solvent of C_2-C_4 (e.g. ethanol), dissolved, and *filtered-eliminating solid particles from the mixture* before proceeding with the incorporation of other components. Thereby, "dissolving 10% to 50% w/w of ritonavir in an excess amount of an alcoholic solvent" is not supported in the specification as particles of ritonavir are removed during the filtration process which affects the resulting amount of ritonavir and the final amount of ritonavir. As a result, the amounts used during the process are not the same as the final product. There is no support in the disclosure for the range claimed as the starting amount, nor any support for specific amounts for the materials used in the method of making. There is a general disclosure of the steps and examples of the final composition but not of the starting material amounts or ranges.

Additionally, the amount of solvent along with the distillation and addition to correct the "final weight" also will affect the amount of starting material as it is likely that the artisan will need a greater amount for the components than what is present in the

final product, Whereby there is no disclosure for the starting amounts for the components of the composition for the method claimed.

For purposes of examination, any amount is acceptable.

8. Claims 26-27, 30, 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of making a ritonavir composition wherein the an "excess amount of an alcoholic solvent of C_2-C_4" is used. There is no written description for the term. There is support for the term "sufficient amount" on Page 17, however the term "sufficient" is unclear as to how much solvent is used. There is inadequate disclosure for the phrase "excess amount of an alcoholic solvent of C_2-C_4".

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 26-27, 30, 32-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The methods of manufacture steps do not state a specific concentration, weight, or final product form as an endpoint. This makes the claims indefinite as to what is the invention and leaves the metes and bounds of the claim unclear. Thereby the claims are rejected.

11. Claims 26-27, 30, 32-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "excess amount" is also unclear as to how much solvent is used. This makes the claims indefinite as to what is the invention and leaves the metes and bounds of the claim unclear. Thereby the claims are rejected.

For purposes of examination, any amount is acceptable.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 37-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari et al. (U.S. Pat. # 6,232,333) in view of Bailey et al. (U.S. Pat. # 6,008,228).

It is noted that the claims recite product by process limitations wherein the only limitation for examination is the final product which is viewed as product/composition claims by the office.

Lipari et al. teaches a composition of proteinase inhibitors, specifically ritonavir, that have increased bioavailability. The composition is comprised of a protease inhibitor (ritonavir), fatty acid, alcoholic solvents, surfactants, and antioxidants.

The preferred ranges for the proteinase inhibitor (ritonavir) are from about 1 to about 50% and most preferably from about 15% to about 40% (see full document,

specifically Col.8, lines 64-68, Col.9, lines 1-17, Col. 22 Example 7, 10) fulfilling the claims.

The fatty acid would be utilized in the preferred range of about 20% to about 99%.

The alcoholic solvents used include ethanol, propylene glycol, benzyl alcohol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400/PEG400 (also an emulsion stabilizer), and mixtures thereof to a preferred range of about 0% to about 15%, thereby fulfilling the claims. Specifically a mixture of ethanol and propylene glycol is recited to be preferably from about 10 to about 15% (Col. 8, lines 26-35, Col. 9, lines 17-43 and 60-68, Col. 10, lines 25-55, Col. 30, and Example 35).

The surfactants taught included polyoxyl 35 castor oil (Cremophor ® EL), polyethylene glycol 40 hydrogenated castor oil (Cremophor ® RH 40), Tween ® 20, 40, 60, and 80 (polysorbates/polyoxythylene (20) sorbitan mono fatty acid esters). The preferred range for the surfactants taught are from about 0% to about 40% and preferably from about 5 to about 10% (Col. 8, lines 35-63, Col. 9, lines 30-36, Col. 10, lines 25-55). Thereby fulfilling the limitations of the claims.

The antioxidants taught include BHT (butylated hydroxytoluene) and ascorbic acid, which is also a polarity corrector, in a preferred range of about 0.01% to about 0.08% (Col. 8, lines 8-12), Col.11, lines 33-40).

Lipari et al. does not expressly teach the use of a mono/diglyceride mixture and the range of 20-40% or the specific use and range of PEG 400.

Bailey et al. teaches the use of monoglycerides and specifically the preferred mixture of medium chain mono/diglycerides C_8-C_{10} for proteinase inhibitor compositions, including ritonavir. Bailey teaches that proteinase inhibitors, being hydrophobic and/or lipophilic have difficulty being absorbed, especially due to crystal forms (polymorphs).

Bailey teaches that certain classes of glycerides used as carriers for formulation assist in alleviating these inadequacies. In fact they achieve better absorption and enhanced bioavailability with good stability/shelf life over a long period of time. The preferred combination was a mixture of medium chain mono/diglycerides C_8-C_{10} that was commercially available under many names including CAMPUL MCM®. The glycerides are derived from medium chain C_8-C_{10} fatty acids (Abstract, Col. 1 line 54-Col. 2 line 23-62, Col. 3, lines 5-68, Col. 4, lines 1-45, Col.16, lines 5-68, Col. 17, line 16-35, Col. 19 line 45- Col. 20 line 28, line 53-Col. 22 line 68).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the fatty acid for a mixture of medium chain mono/diglycerides C_8-C_{10}, as suggested by Bailey, and produce the instant invention as glycerides are derived from fatty acids, have equivalent properties, and are routinely substituted dependent on the desired physical properties of the composition. It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions and arrive at the range of 20-40% for the mixture of medium chain mono/diglycerides C_8-C_{10} because the range for the fatty acids as taught by Lipari are from about 20% to about 99%. Routine experimentation and optimization

in the art when the general conditions of a claim are disclosed in the prior art is not inventive or patentably distinct.

One of ordinary skill in the art would have been motivated to do this because increase bioavailability and shelf life/stability of a ritonavir composition is desirable since the drug is known to have difficulty with crystal forms, stability, and bioavailability.

Bailey also teaches the specific ranges for the use of PEG 400 of 0-30% by weight for compositions containing about 120mg to about 300mg of proteinase inhibitor.

PEG is commonly used in substitution for fats since it has greater physical stability, so storage is better, they do not become rancid, and the release of the drug is not due to the melting point. In conjunction, PEG's can be more reactive than fats so an increased amount of antioxidant/polarity corrector may be needed and Bailey suggests a range of 0.01% to 0.5% that one of skill in the art would utilize as needed if the amounts taught by Lipari needed modification.

PEG is known to be used to enhance the aqueous solubility of poorly soluble compounds, like ritonavir, and is commonly used as a water-miscible solvent for compositions for gelatin capsules. They are also used for adjusting the viscosity of compositions, suspending agent, and emulsion stabilizers (see sheets on Polyethylene Glycol from Handbook of Pharmaceutical Excipients).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize a larger percentage of PEG 400, as suggested by Bailey, and produce the instant invention. The composition taught by Lipari utilized fatty

acids on the range of about 20% to about 99%, and with the substitution of the CAMPUL® for the fatty acid, increased amounts of PEG 400 would be utilized, as suggested by Bailey, to compensate and provide added solubility for the ritonavir as a solvent, emulsion stabilizer, and viscosity agent which would be adjusted by one of skill in the art to the desired consistency. It would also provide greater stability for storage and better bioavailability having consistent release not subject to melting points in conjunction to improved properties of the CAMPUL ®.

One of ordinary skill in the art would have been motivated to do this because ritonavir is known for difficult bioavailability and stability so any modification to improve stability, storage, and bioavailability would be desirable. This would reduce costs and improves profits.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 26-27, 30, 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari in view of Bailey as applied to claims 37-45 above, and further in view of CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques.

Lipari teaches the preparation of a ritonavir composition by combining a fatty acid and pharmaceutically acceptable alcohols.

They are mixed at room temperature (about 33°C). The antioxidants are added, mixed, and the protease inhibitor (ritonavir) is added and stirred until dissolved. Surfactant is then added, mixed, filtered, and then the appropriate volume (e.g. ritonavir 200mg) of the mixture corresponding to the desired dose is formulated into capsules (Col 21, lines 10-30, Col. 22, lines 25-55, Example 7, Col. 23, lines 35-68, Col. 30, Example 35). Bailey teaches the use of mono/diglycerides and its substitution for fatty acids are discussed above. Note that reversal/modification of the order of known steps of manufacture that produces the same product is not patentable.

Lipari in view of Bailey does not expressly teach the use of vacuum distillation.

CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques teaches vacuum distillation.

Vacuum distillation/evaporation is a common and basic process for removing solvent, condensing, and purifying a compound (ritonavir). The practice is used industrially and laboratories commonly in the form of the rotary evaporator. Being a basic and know skill and process, the technique is taught in school lab chemistry courses.

It is especially valuable in distilling compounds that might undergo decomposition on heating at atmospheric pressure, as it is used with or without heat, and used to remove solvents from the mixture without damaging the product (see Wikipedia sheets

specific to vacuum distillation and CUBoulder sheets specific to vacuum distillation and solvent removal).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize vacuum distillation to thermal degradation of the drug, as suggested by CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques to produce the instant invention as ritonavir is known, by applicants own admission, to have thermal degradation at higher temperatures.

One of ordinary skill in the art would have been motivated to do this because it would be a more stable method for producing the ritonavir composition and the method produces less residue build up which is important in commercial applications where temperature transfer is produced with heat exchangers (see Wikipedia sheets specific to vacuum distillation and CUBoulder sheets specific to vacuum distillation and solvent removal).

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

15. Claims 26-36 are rejected under 35 U.S.C. 112, second paragraph, for indefiniteness with respect to the methods of manufacture that do not state a specific concentration, weight, or final product form as an endpoint.

Claim 28-29, 31, 36 are cancelled, the rejection is moot.

Applicant's arguments see page 13 filed 6/3/2008 have been fully considered but they are not persuasive. Applicant's amendments to overcome the rejection are subject to the new matter rejections and indefinite rejections addressed above. It is also not persuasive as the claims are amended to recite steps where there is no reasonable direction stated in the claims for the amounts used or the recitation of "correcting the final weight" of the composition when there is no specific final weight disclosed in the claims. One would not be apprised of the metes and bounds of the invention as it is directed to make a composition where the specifics of the composition are not recited.

The rejection is maintained.

16. The rejection of claims 1-25 are moot as the claims are cancelled. Applicant's arguments (Page 8-10) in regards to Lipari et al. (U.S. Pat. # 6,232,333) in view of Bailey et al. (U.S. Pat. # 6,008,228) are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Additionally, the arguments in regards to Bailey is not commensurate in scope with the rejection as the Bailey reference was used to show the teaching that incorporation of monoglycerides and specifically the preferred mixture of medium chain mono/diglycerides C_8-C_{10} for proteinase inhibitor compositions, including ritonavir, assist in alleviating the inadequacies of hydrophobicity and absorption, and in fact achieve better absorption and enhanced bioavailability with good stability/shelf life over a long period of time. The arguments are directed to the entire formulation in Bailey and the examples for saquinavir. The primary reference is Lipari which addresses the formulation, not Bailey, and is not commensurate in scope with the rejection or the claims.

This also goes to the declaration submitted which has been considered but is not persuasive. The declaration goes to the formulation of Bailey and not the formulation of Lipari which is presented in the rejection. The declaration is also not commensurate in scope with the claims as the declaration and comparative goes to polymorphs which are not presented in the claims or the specification and to the Bailey formulation, not the Lipari formulation and is not persuasive.

Applicant's arguments in regards to the content of monoglycerides (50-62%) in the mixture for ALKONINE verses those presented in Bailey is not persuasive as it is

not commensurate in scope with the claims. The claims only state a mixture of medium chain mono/diglycerides C_8-C_{10}, not the percentage. However, it is noted that Bailey teaches several commercial forms of the mixture, preferably CAPMUL MCM with at least 70% monoglycerides, and CAPMUL MCM90 has between about 83-about 95% monoglycerides, but Bailey also taught IMWITTOR with a composition of about 50%monoglycerides similar to AKOLINE (Col. 19 line 45-Col. 20 line 48).

17. Claims 26-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari in view of Bailey as applied to claims 1-21 above, and further in view of CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques.

Claim 28-29, 31, 36 are cancelled, the rejection is moot.

Applicant's arguments see page 10-13 filed 6/3/2008 have been fully considered but they are not persuasive. Applicant's arguments that there is complete dissolution and the solution is microcrystal free form at a high concentration are not persuasive as it is not commensurate with the scope of the claims. First, the claims do not recited complete dissolution, second the next step is filtration of "solid particles" which would be *contrary* to the assertion of complete dissolution, third there is no end point for the claims so the argument for a high concentration (which is relative) is not commensurate in scope with the claims, fourth the argument in regards of the polymorphic forms are not commensurate in scope with the claims as it is not claimed and polymorphs are crystalline forms and when dissolved in solution are not polymorphic, Fifth the argument of motivation for dissolving ritonavir under low temperatures is not persuasive as Lipari teaches the same temperature ranges for ritonavir.

The rejection is maintained.

Conclusion

18. Claims 26-27, 30, 32-35, 37-45 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
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